Docket Number: 50623.00266

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application Of: Examiner: Sheeba Ahmed

Stephen Dirk Pacetti Art Unit: 1773

Serial No: 10/606,711

Filed: June 26, 2003

For: COATINGS FOR IMPLANTABLE MEDICAL DEVICES COMPRISING HYDROPHOBIC AND HYDROPHILIC POLYMERS

DECLARATION UNDER 37 CFR § 1.131

I, Stephen D. Pacetti, declare as follows:

1. The application identified above was filed on June 26, 2003.

2. I conceived of or invented the subject matter of the application identified above in the United States prior to February 23, 2003. See Appendix A – redacted invention disclosure form.

3. I provided this invention disclosure form to our patent attorneys, through the management of Advanced Cardiovascular Systems, Inc., the assignee of this patent application on April October 9, 2002. Advanced Cardiovascular Systems, Inc. approved the invention for filing a patent application. Our patent attorneys filed the application on June 26, 2003.

4. I further declare that all statements made herein of our own knowledge are true and that all statements made upon information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are

punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Executed at San Jose, California on this 6th day of July, 2006.

By: Stephen Pacetti
Stephen D. Pacetti

APPENDIX A

GUIDANT CONFIDENTIAL & PRIVILEGED

For Legal Department Use Only
Docket No.: 3800
Date Assigned: 10/10/02
Date Discl. Rec'd: OCT 09 2002

Drug Delivery

INVENTION DISCLOSURE FORM

ADVANCED CARDIOVASCULAR SYSTEMS, INC.

This is a form for disclosing ideas and inventions to the Guidant Legal Department for patent consideration. This form may be used before experimental work has been done. While some of the requested information may not be available at this time, include as much information as you can about the invention. Attach additional sheets if necessary, and sign and date each sheet. Additional information will be requested later.

Please complete each indicated area and return to Intellectual Property Paralegal, Guidant Vascular Intervention Group, 3200 Lakeside Drive, Santa Clara, CA 95052, and a copy to the R&D Director.

1. DESCRIPTIVE TITLE OF THE INVENTION: **Non-Fouling and Protective Coatings for Implantable Medical Devices**

Inventors initials:
1 S.P. 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____

INTRODUCTION

A current paradigm in biomaterials research is the control of protein adsorption on the implant surface. Uncontrolled protein adsorption, leading to mixed layer of partially denatured proteins, is a hallmark of current biomaterials when implanted. Such a surface presents different cell binding sites from adsorbed plasma proteins such as fibrinogen and immunogloblulin G. Platelets and inflammatory cells such as monocyte/macrophages and neutrophils adhere to these surfaces. When so activated, they secret a wide variety of proinflammatory and proliferative factors including PDGF, TNF-α, IL-1β, IL-6, IL-8, IL-10, and TGF-β.

These initial protein adhesion events set the stage for thrombosis and the foreign body response. Several strategies have been put forth to try to mitigate these undesirable surface adhesion events. One approach is to mimic the cell membrane of, for example, endothelial cells. This requires providing the surface with some sort of lipid-bilayer, decorated with glycosaminoglycans, and cellular binding proteins or peptides such as integrins. This has proved to be a complex problem. A simpler strategy is to simply make to surface "stealthy" so that it does not adsorb any proteins. Another name for this type of surface is "non-fouling". If no proteins adsorb, it is known that cellular adhesion and activation is reduced.

Many non-fouling substances have been utilized including poly(ethylene glycol) (PEG), poly(ethylene oxide), hyaluronic acid, dextran, dextrin, dextran sulfate, and heparin. These materials are water-soluble and when cross-linked, or surface immobilized, they form a hydrogel layer on the implant surface. To a first approximation, this hydrogel layer resist protein adhesion by virtue of its extremely low hydrogel/water interfacial tension. There is no thermodynamic driving force for proteins to occupy this interface. Additionally, these materials resist fouling due to their lack of positive charge and water binding properties. For molecules such as PEG, the parameters of surface packing density, and chain length, are known that resist protein adsorption.

The leading configuration for drug eluting stents is a polymer coating on a metal stent. The polymer acts as a reservoir for the drug and, if necessary, can control the drug release rate. Adding a non-fouling surface to a polymer coated drug eluting stent is desirable as it should improve hemocompatibility and mitigate the foreign body response. There are several approaches to adding a surface of PEG or hyaluronic acid to a stent coating. Many of them require grafting with radiation or crosslinking with UV radiation. It is not clear if the drug would be adversely affected by exposure to high levels of gamma radiation or UV. Other approaches require soaking the stent in baths that place the coating on the surface. Immersion of DES stents into baths of water or, more particularly, organic solvents will result in drug leaching into the bath.

Blending PEG, hyaluronic acid, or other non-fouling molecule into the stent coating polymer, and then spraying it on as a topcoat is an attractive choice. It is simple and uses existing technology. Issues include the compatibility of the additive with the coating polymer, mechanical properties of the blend, leaching of the additive into tissue or blood, and whether the additive is actually surface active. For example, optical microscopy studies have indicated that 10% PEG 20K by weight appears to be miscible with EVAL, but at a 25% loading, the PEG phase separates. Phase separated PEG will weaken the EVAL and should leach from the polymer readily. In addition, crude contact angle studies have indicated that PEG blended with EVAL at a 10% loading is not necessarily available at the coating surface after baking. In the attached report, contact angle measurements without any prehydration show 10/90 PEG/EVAL to not that different from pure EVAL.

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Another issue with polymer coated stents, is one of surface contamination during manufacturing. Unlike a metal surfaces, polymer surfaces can be tacky, particularly right after coating. A variety of debris has been observed adhering to DES stents after manufacturing. We have to ubiquitous white fibers, the fairly common blue fibers, and various specks and blobs of contamination. Semisolid and liquid contamination in the form of silicones, oils, and skin oils are also a possibility. The consequences of surface contamination on stents are well known and include inflammation, granuloma formation, and greater neointimal formation. The 3 month Wayne implant demonstrated some granuloma in the control and coated arm.

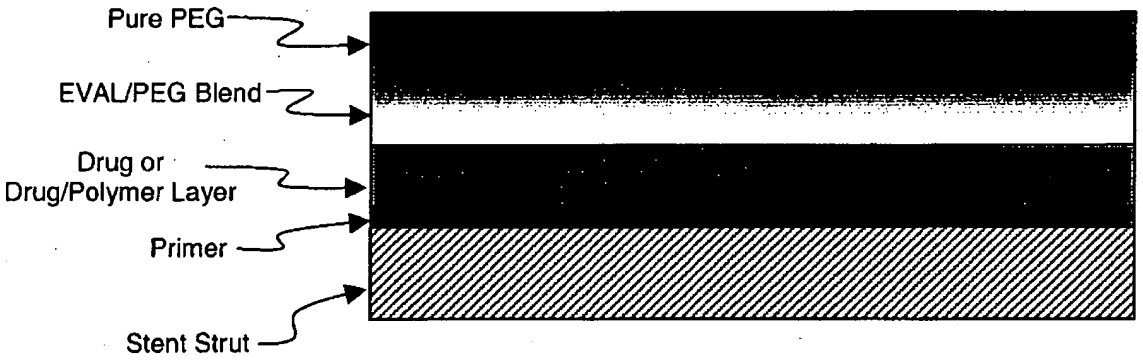
DISCLOSURE

(a) What is disclosed is a polymer coated, drug eluting stent that has the following two outermost layers:

Topmost Layer: This layer consists of a water soluble, biocompatible polymer, which is intended to protect the underlying layer, dissolve in vivo, and be compatible with a hydrophilic additive in the underlying layer

Underlying Layer: This layer is intended to be permanent and consists of a blend of a structural polymer, such as EVAL, and a non-fouling, hydrophilic additive, such as PEG. This underlying layer can be a "topcoat" for controlling drug release, or it may be exist only to present a non-fouling surface to the in-vivo environment after the topmost layer has dissolved.

A schematic of this coating configuration is shown below. In this diagram, the topmost layer is of PEG. The underlying layer is a blend of PEG with EVAL.



The gradient in color between the topmost layer and underlying layer is intended to indicate a gradient of PEG concentration. The pure PEG of the topmost layer should induce an enrichment of PEG at the interface between the two layers.

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In studies so far, blending PEG with EVAL did not necessarily assure a large concentration of PEG at the surface. One explanation for this is that these films were made by solvent casting. When casting from a solvent, the component that minimizes the surface free energy will migrate to the surface. This is because the coatings are dried in air. If they were dried in water, the situation would be different. Minimizing surface free energy is the mechanism by which surfactants work. In the case of solvent blends, low surface tension solvents, such as pentane or ethanol would preferentially be at the surface instead of high surface tension solvents such as DMAC. As the solvent concentration diminishes, the surface tension, or surface free energy of the dissolved polymers comes into play. PEG has a high surface tension of 43 dyne/cm.[1] If the surface free energy of EVAL is less than this, then the EVAL will be preferentially at the surface. With more hydrophobic, low surface free energy polymers, such as Kynar, the driving force is even greater. So the underlying layer, dried in an air atmosphere may not have a surface rich in the hydrophilic additive. However, if a topmost layer is coated on top consisting of pure hydrophilic additive, PEG for example, or another very polar, hydrophilic material then the interface between the underlying layer and the topmost layer will be enriched with the hydrophilic additive. More specifically, the PEG of the underlying layer would favorable interact with the pure PEG of the topmost layer creating a very PEG rich interface. When this system is immersed in water, the topmost layer dissolves away revealing the surface of the underlying layer. This surface is PEG enriched and will remain so because it is now exposed to the very polar aqueous environment. The surface free energy of PEG exposed to air is 43 dyne/cm, but the surface free energy of the PEG/water interface is very low, less than 1 dyne/cm. In fact, if the PEG is not immobilized it dissolves away. The PEG will be immobilized in the surface of the underlying layer by entanglement. With mobile polymers above their Tg, such as PBMA, the PEG will work its way loose at some slow rate. With a higher Tg polymer such as EVAL or Butvar, the PEG will be much less mobile and will only leach very slowly, if at all. If the polymer has some crystallinity, which EVAL and Elasteon have, and portions of the PEG molecules at the surface are trapped in crystalline regions, then the PEG would be very long lived.

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Polymers with a high degree of biocompatibility, a history of medical use, and that can also be cleared by the kidneys are appropriate for use in a topmost layer. The cutoff for renal clearance is known to be in the range of 20-50K depending on the size of the random coil in aqueous solution. Example polymers are dextran, hyaluronic acid, PEG, PEO, poly(vinyl alcohol), Pluronic surfactants, heparin, chitosan, sulfonated polystyrene, and HEMA.

An alternate coating configuration is also possible that is simpler, but less flexible in capabilities. In this scheme, there is still a hydrophilic, water soluble topmost layer. A schematic is shown below.

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Inventors initials:
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Witness Signature (not required)

Read and understood the completed Invention Disclosure Form

Houdin Dehnad
Printed Name

Houdin Dehnad Oct 9, 02
Signature Date

Inventors initials:
1 S.P. 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____

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5/14/02

A Water Soluble Coating for a Stent Surface to Promote Surface Enrichment of Hydrophilic Groups for the Underlying Surface Layer

Various strategies exist to render stent surfaces "non-fouling", "non-thrombogenic", and anti-inflammatory by placement of hydrophilic, non-fouling groups. A favorite molecule for this purpose is poly (ethylene glycol). PEG can be immobilized to surface by several methods. However, surface immobilization can require additional steps or complex steps that are not compatible with a drug contained in underlying layers. Another strategy is to simply add PEG to the topcoat polymer. The hope is that adding PEG will lead to a PEG surface. There are several problems with this strategy:

1. PEG may have limited miscibility with the topcoat polymer. If PEG is added to the point where it phase separates the mechanical properties can be compromised, the drug release rate can be high, and the surface can be rough.

2. If, for example, the formulation is 10% by wt. PEG in the topcoat polymer, then the surface may be only 10% PEG unless there is a large tendency for surface enrichment by the PEG. A surface that is only 10% PEG will not be non-fouling.

There has been expressed the hope that added PEG will bloom to the surface. During a solvent coating process, there is a great deal of polymer mobility. The components that will migrate to the surface are the components that will minimize the surface free energy. If one adds a silicone or a fluoropolymer to most other polymers,

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SIGNATURE S Stephen Pacetti DATE 5/13/02

DISCLOSED TO AND UNDERSTOOD BY Andrew Long DATE 5/30/02 WITNESS DATE

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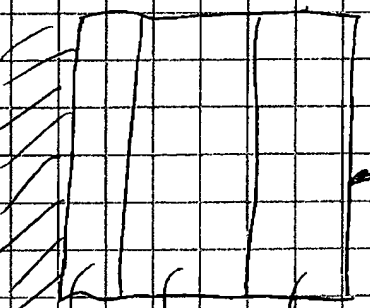
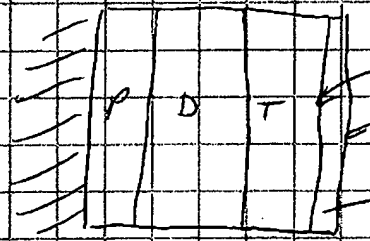
it is true that the silicone or fluorocarbon will enrich the surface. These additives have a very low surface free energy and will almost always enrich the surface. If one added 5% silicone to PBMA, we can be certain that upon air drying of such a coating, the resultant surface will be all silicone. However, when PEG is simply added to PBMA the situation will be different. PEG is not a low surface energy material. The n-butyl groups of PBMA though are the lowest surface energy groups of the blend. PBMA+PEG that is air dried will have a surface of n-butyl groups. Upon exposure to blood, the surface will absorb proteins. One could argue, that in the aqueous environment the PBMA-PEG surface will rearrange to expose PEG to the surface. Energetically this is favorable. However, high mw PEG will diffuse very slowly through PBMA. The rearrangement of the surface will take time while protein adsorption is fast, taking seconds or less. Now Consider the system below:



One can add PEG to the topcoat formulation. The PEG will likely not be at the surface during drying but will be dispersed throughout the bulk.

If we coated a very polar water soluble polymer on top of the PEG-Topcoat, then the interface between the two layers will be different



SIGNATURE Stephen Paretti DATE 5/13/02

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72 **TITLE** Disclosure on a Heparin Coating for a Stent Using Fractionated Heparin

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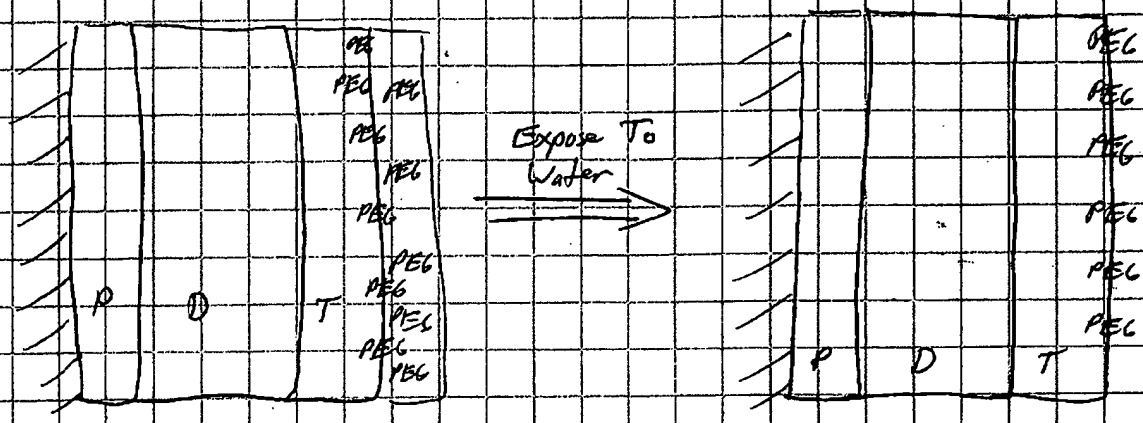
This final, hydrophilic coating can be very thin. Only enough is needed for coverage. When implanted, it will rapidly dissolve away, leaving a PEG enriched surface



This extra coating step assures a final PEG surface for the stent upon exposure to blood. All of the coating steps can be done by spray coating.

Suitable materials for the final, dissolvable layer are PEG, PEO, hyaluronic acid, PVP, chondroitan sulfate, glycosamino-glycans, dextran, dextrin, dextran sulfate, cellubiosics, cellulose acetate, carboxymethyl cellulose, cellulose acetate butyrate, chitosan and other hydrogels.

5/14/02 A Heparin coating for a Stent Using Fractionated Heparin enriched in the Antithrombin binding site

Coat a stent with tethered antithrombin - heparin covalent complex. This complex has higher anti-thrombin and anti-factor Xa activities compared to unfractionated heparin.

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SCIENTIFIC BINDERY PRODUCTIONS CHICAGO 60605 MADE IN USA

SIGNATURE Stephen Pacetti **DATE** 5/23/02

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Miscibility of PEG 20K and Povidone 29K with EVAL and PBMA

Conducted by the DDT Group – Dept 1403

R&D Technician	Bozena Maslanka	Date
R&D Engineer	Stephen Pacetti	Date

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Miscibility of PEG 20K and Povidone 29K with EVAL and PBMA

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Materials:	• PVP (Polyvinylpyrrolidone) Average Mw 29,000 100gm P/N 23425-7 lot#06306PO • PEG (Polyethylene Glycol) Average Mw20,000 P/N 22568 lot#521420 • Fat free E151A EVAL • DMAC RM2031749 lot#99232035 • PBMA lot#649000 • MeOH P/N 27,0474 lot#PO103620MO • EtOH RM2034286 lot#99194913 • IPA P/N PX1838-1 lot#41355203 • Pipet • glass slides • vials 20cc • jars • polarization microscope • oven • Scale

Test Procedure:	Make a 10% stock solution of fat free E151A EVAL in DMAC.
	Make a 10% stock solution of PBMA in DMAC.
1st set:	Make the following solutions. All solutions will be 10 g total. Use cleanest solvents we have. A. 2/98 PEG /EVAL at 5% solids in DMAC B. 5/95 PEG /EVAL at 5% solids in DMAC C. 10/90 PEG /EVAL at 5% solids in DMAC D. 25/75 PEG /EVAL at 5% solids in DMAC E. 2/98 PVP /EVAL at 5% solids in DMAC F. 5/95 PVP /EVAL at 5% solids in DMAC G. 10/90 PVP /EVAL at 5% solids in DMAC H. 25/75 PVP /EVAL at 5% solids in DMAC I. 2/98 PVP /PBMA at 5% solids in 50/50 MeOH/DMAC J. 5/95 PVP /PBMA at 5% solids in 50/50 MeOH/DMAC K. 10/90 PVP /PBMA at 5% solids in 50/50 MeOH/DMAC L. 25/75 PVP /PBMA at 5% solids in 50/50 MeOH/DMAC M. 100% EVAL at 5% solids in DMAC N. 100% PBMA at 5% solids in 50/50 MeOH/DMAC
2nd set: (repeat)	Make the following solutions. All solutions will be 10 g total. Use cleanest solvents we have. A A. 2/98 PVP/PBMA at 5% solids in 100% 1,1,2-trichloroethane PVP 0.01 gm TCE 9.50 gm PBMA 0.49 gm A B. 5/98 PVP/PBMA at 5% solids in 100% 1,1,2-trichloroethane PVP 0.025 gm TCE 9.50 gm PBMA 0.475 gm A C. 10/90 PVP/PBMA at 5% solids in 100% 1,1,2-trichloroethane PVP 0.05 gm TCE 9.50 gm PBMA 0.45 gm

	A D. 25/75 PVP/PBMA at 5% solids in 100% 1,1,2-trichloroethane PVP 0.125 gm TCE 9.50 gm PBMA 0.375 gm
	Label a glass slide for each solution. Place the glass slides in a glass tray and place the tray in the oven at 60C. Pipet some of each solution onto its glass slide. Don't let solutions run off or dissolve your labeling. When all are dispensed, raise oven temp to 80C and bake for 2 hours.
	Inspect the glass slides under the cross polarization microscope. Look for phase separation. Take pictures if there is anything to see.
	Measure the contact angle of Milli-Q water with some of the coated slides you have made.

Acceptance Criteria:	Non-fouling surface of PEG and PVP molecules with polymers of interest.

Results: The EVAL and PBMA stock solution was mixed per MPI 2029382 Rev H

Group	Target Batch Size (g)	Solids Target (g)	Solvent DMAC (g)	Date mixed
EVAL Stock	50.00	5.00	45.00	7/30/02
PBMA Stock	50.00	5.00	45.00	8/01/02

Table 1

The following solution were mixed as listed below Table 2 & Table 3

Solution formulation	Desired amount of coating solution (grams)	Desired % of solids	What is % of solids (wt Solid1 + wt solid2) of desire coating solution (grams)	Fraction of first polymer in solids	% Of second polymer in solids	Amount of first solid in grams	Name of first solid	How much of second Solid	Fraction of second polymer in stock solution	Amount of Stock solution in grams	Name of 2nd polymer stock solution	Amount of DMAC to add to finished solution (grams)
A	10	5	0.5	0.02	0.98	0.01	PEG	0.490	0.1	4.90	EVAL	5.09
B	10	5	0.5	0.05	0.95	0.025	PEG	0.475	0.1	4.75	EVAL	5.23
C	10	5	0.5	0.1	0.90	0.05	PEG	0.450	0.1	4.50	EVAL	5.45
D	10	5	0.5	0.25	0.75	0.125	PEG	0.375	0.1	3.75	EVAL	6.13
E	10	5	0.5	0.05	0.95	0.03	PVP	0.475	0.1	4.75	EVAL	5.23
F	10	5	0.5	0.1	0.90	0.050	PVP	0.450	0.1	4.50	EVAL	5.45
G	10	5	0.5	0.25	0.75	0.13	PVP	0.375	0.1	3.75	EVAL	6.13
H	10	5	0.5	0.25	0.75	0.125	PVP	0.375	0.1	3.75	EVAL	6.13
M	10	5	0.5	0	1.00	0.00	EVAL	0.500	0.1	5.00	EVAL	5.00

Table 2

Solution formulation	Desired amount of coating solution (grams)	Desired % of solids	What is % of solids (wt Solid 1 + wt solid2) of desire coating solution (grams)	Fraction of first polymer in solids	% Of second polymer in solids	Amount of first solid in grams	Name of first solid	How much of second Solid	Fraction of second polymer in stock solution	Amount of Stock solution in grams	Name of 2nd polymer stock solution	Amount of DMAC to add to finished solution (grams)	Amount of IPA to add to finished solution (grams)
I	10	5	0.5	0.02	0.98	0.01	PVP	0.490	0.1	4.90	PBMA	0.34	4.75
J	10	5	0.5	0.05	0.95	0.025	PVP	0.475	0.1	4.75	PBMA	0.48	4.75
K	10	5	0.5	0.1	0.90	0.05	PVP	0.450	0.1	4.50	PBMA	0.70	4.75
L	10	5	0.5	0.25	0.75	0.125	PVP	0.375	0.1	3.75	PBMA	1.38	4.75
N	10	5	0.5	0	1.00	0	PBMA	0.500	0.1	5.00	PBMA	0.25	4.75

Table 3

When mixing formula I the solution became clumpy. The formula I was mixed again substituting MeOH for EtOH with same results. The formula was mixed once again substituting EtOH for IPA. With IPA the solution was clear and the remaining J through N was mixed with IPA.

When mixing solution A through D the PEG was added as the last component and during mixing of the solution it turned murky color. The formula A through D was mixed again but in different order. The PEG was mixed with DMAC until it dissolved and EVAL stock was added last.

Each glass slide was labeled and each of the solution was pipet out onto its glass slide. When all were dispensed, it was placed carefully into the oven and baked at 80 C for 2 hours.

Each glass slide was inspected for phase separation under the cross polarization microscope.

1st set of experiment:

Solution formulation	Desired Solids in Stock Solution	Percentage of solids in solution	Visual observation	Microscope observation Crossed Polarizer
A-2	PEG in EVAL	2/98	Little milky	Homogeneous
B-2	PEG in EVAL	5/95	Little milky	Homogeneous, tiny crystals at edge
C-2	PEG in EVAL	10/90	Milky	Homogeneous in center, crystals at edge
D-2	PEG in EVAL	25/75	Milky	Phase separation, many crystals
E	PVP in EVAL	5/95	Clear	Homogeneous
F	PVP in EVAL	10/90	Clear	Homogeneous
G	PVP in EVAL	25/75	Clear	Homogeneous
H	PVP in EVAL	25/75	Clear	Homogeneous
I	PVP in PBMA	2/98	Rough surface	Homogeneous
J	PVP in PBMA	5/95	Rough surface	Homogeneous
K	PVP in PBMA	10/90	Rough surface	Homogeneous
L	PVP in PBMA	25/75	Rough surface	Homogeneous
M	EVAL CONTROL	100	Clear	Homogeneous
N	PBMA CONTROL	100	Rough surface	Homogeneous

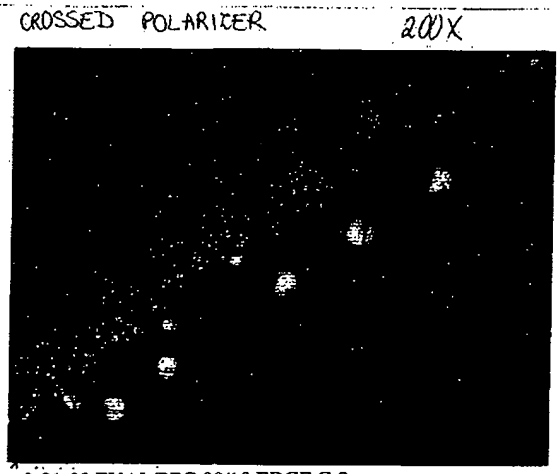
Table 4

2nd set of experiment (repeat)

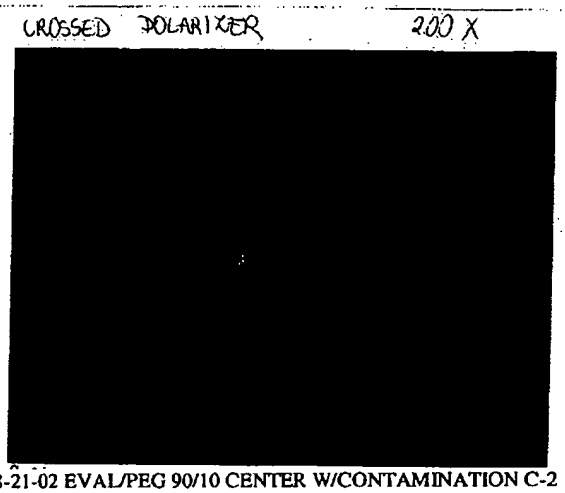
Solution formulation	Desired Solids in Stock Solution	Percentage of solids in solution	Visual observation	Microscope observation Crossed Polarizer
AA	PVP in PBMA	2/98	Little milky	Homogeneous
AB	PVP in PBMA	5/95	Little milky	Homogeneous
AC	PVP in PBMA	10/90	Milky	Homogeneous
AD	PVP in PBMA	25/75	Milky	Homogeneous
A2	PEG in EVAL	2/98	Little milky	Homogeneous
B2	PEG in EVAL	5/95	Little milky	Homogeneous tiny phase separation at edge
C2	PEG in EVAL	10/90	Milky	Homogeneous in center, phase separation at edge
D2	PEG in EVAL	25/75	Milky	Phase separation
E	PVP in EVAL	5/95	Clear	Homogeneous
F	PVP in EVAL	10/90	Clear	Homogeneous
G	PVP in EVAL	25/75	Clear	Homogeneous
M	EVAL CONTROL	100	Clear	Homogeneous

Table 5

Two samples with phase separation were observed and photographed.
Sample C-2 with 10/90 PEG/EVAL the center was homogeneous with tiny phase separations at the edge as shown in Table 5.
Sample D-2 with 25/75 PEG/EVAL the center was homogeneous with phase separations at the edge as shown in Table 6.

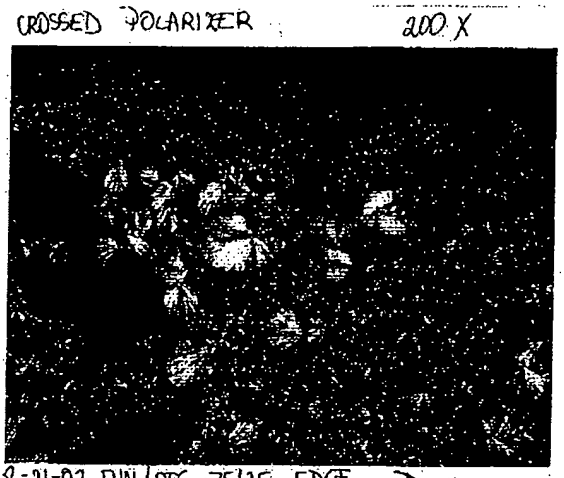


8-21-02 EVAL/PEG 90/10 EDGE C-2



8-21-02 EVAL/PEG 90/10 CENTER W/CONTAMINATION C-2

Table 5



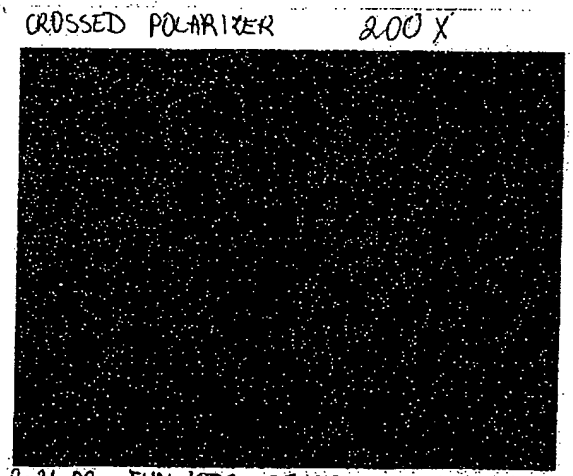


Table 6

Guidant Corporation
3200 Lakeside Drive, Santa Clara, CA 95052
Tel 408. 845-3000 Fax 408. 845-3333
www.guidant.com

Advancing and receding contact angle measurements were taken with a Rame-Hart Goniometer.

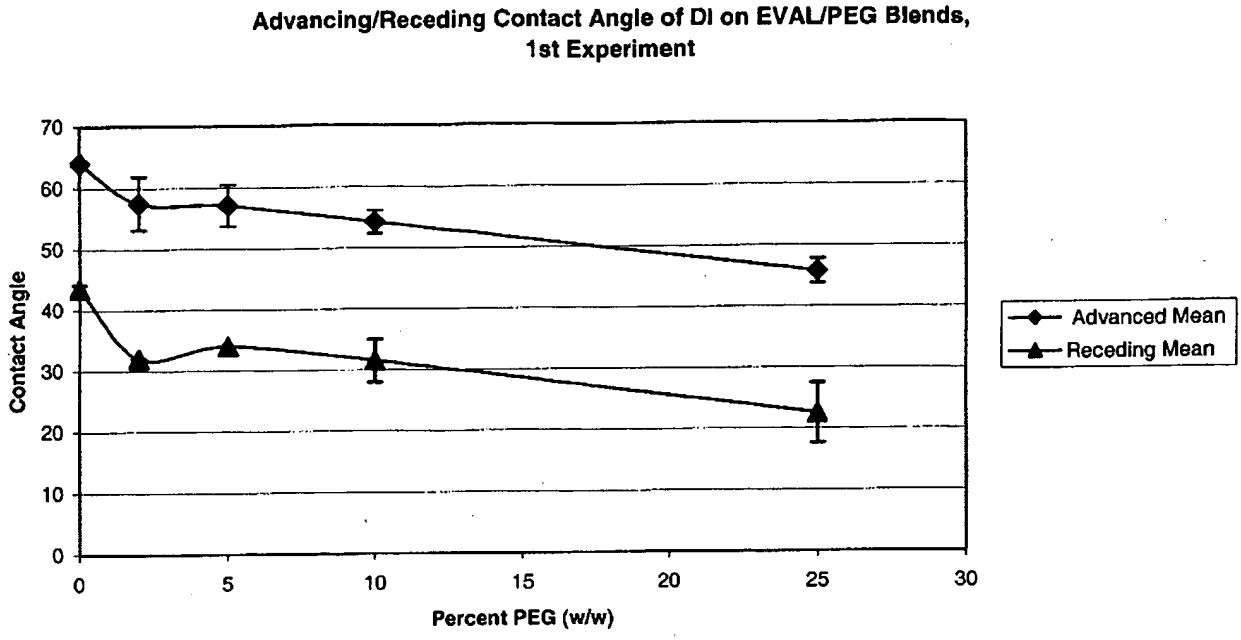


Table 7

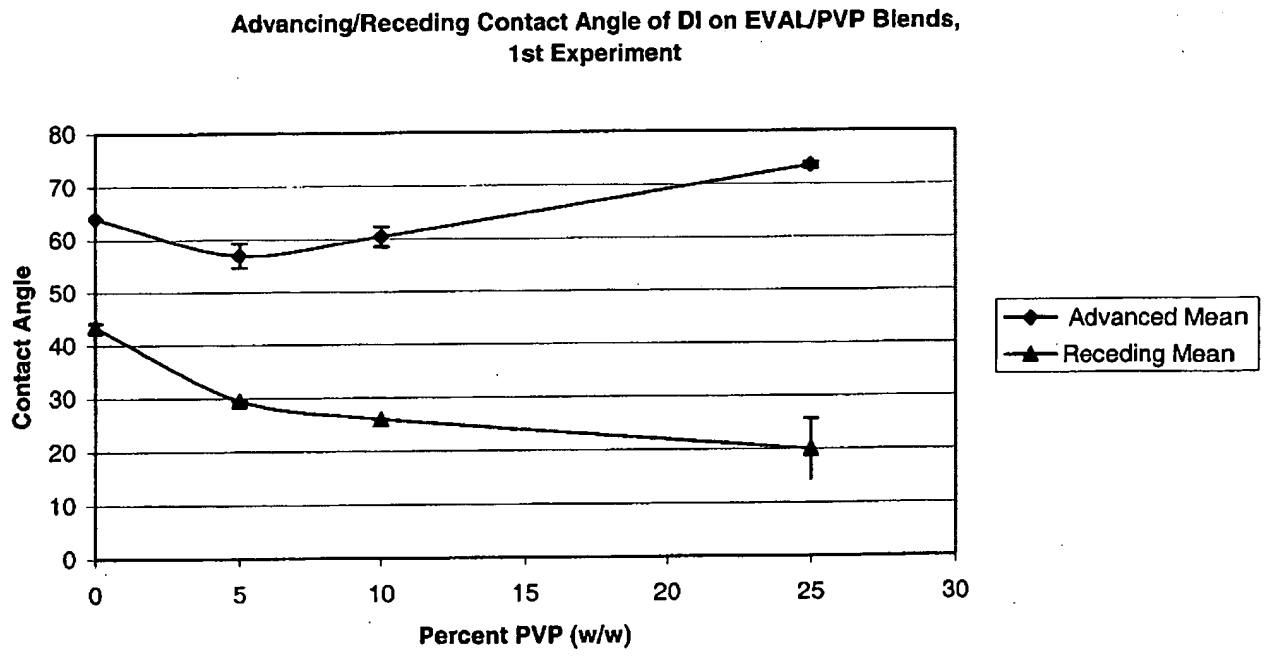


Table 8

A second set of slides were made to repeat contact angle measurements to ensure that it was contamination free.

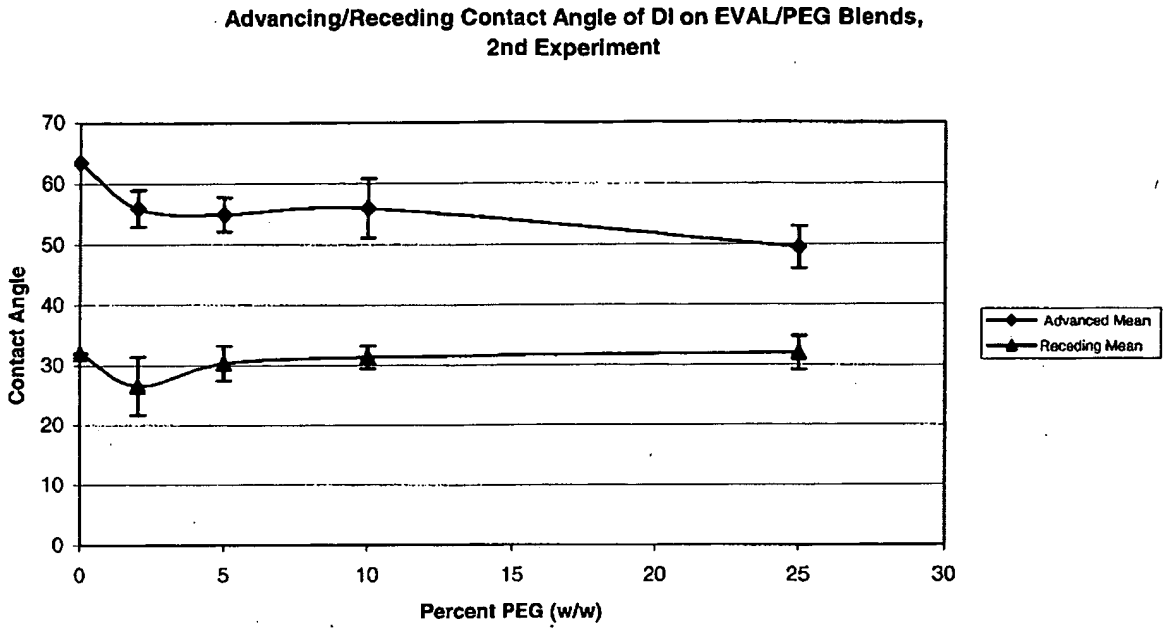


Table 9

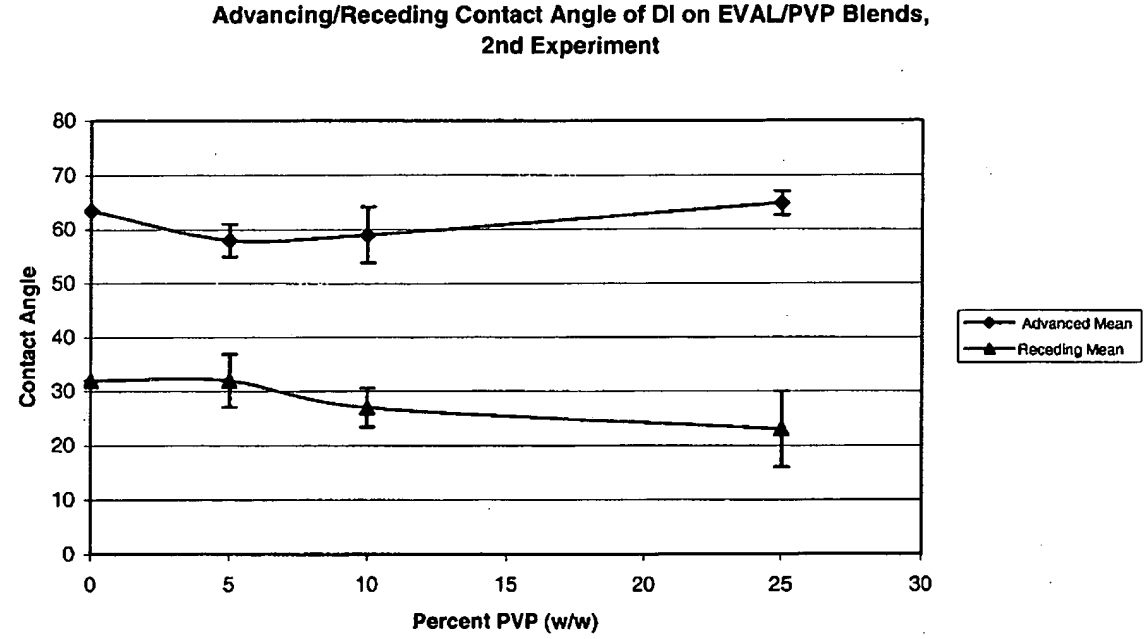


Table 10

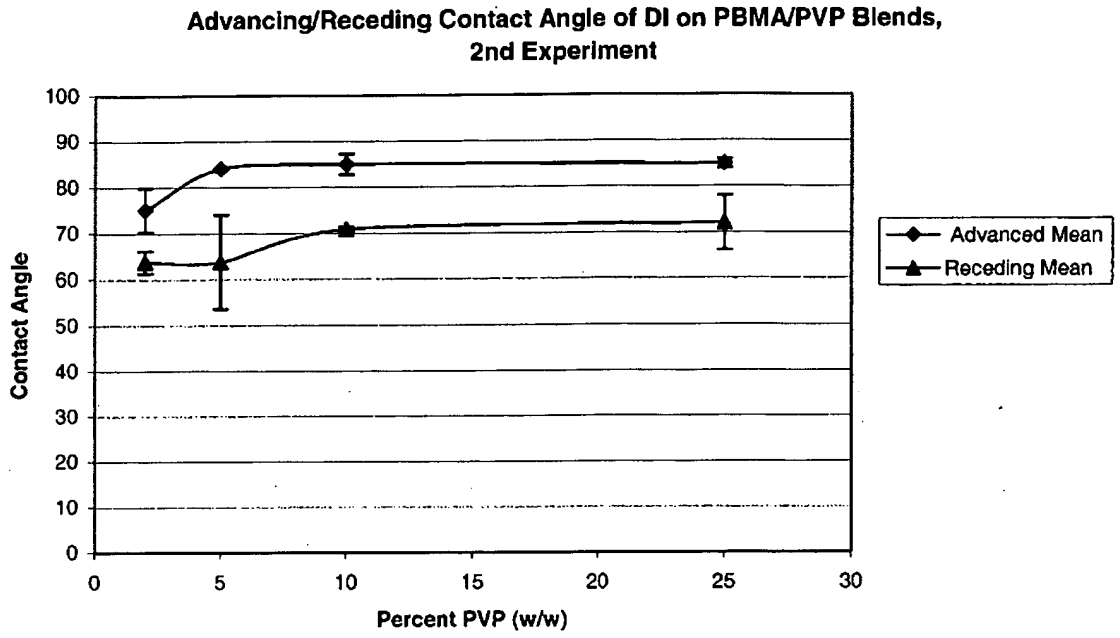


Table 11

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Blends of PVP/EVAL showed slightly different behavior. Increasing levels of PVP actually increased the advancing contact angle. The receding angles were lower and PVP generally lowered the contact angle. In one case 25% PVP decreased the contact angle to 20 degrees, and in the second experiment, it decreased it to 22 degrees.